by Applicants and copies of references named in the form PTO-1449.

In the present Office Action, the Examiner made a number of arguments, objections, and rejections. For clarity, the rejections and objections at issue are set forth by number in the order they are herein addressed:

**I.** Claims 90-106 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention;

**II.** Claims 109-110 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention;

**III.** Claims 111, 113, and 114 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention;

**IV.** Claim 123 is rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention;

**V.** Claim 124 is rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention;

**VI.** Claims 127 and 136 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention; and

**V.** Claims 107-136 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 6,372,427 (hereinafter the '427 patent) in view of U.S. Patent 5,451,503 (hereinafter the '503 patent), in further view of U.S. Patent 5,635,352 (hereinafter the '352 patent), in further view of Cole *et al.* (Cole *et al.*, Analytical Biochemistry 231:309-314 [1995], hereinafter Cole), in further view of Guatelli (Guatelli *et al.*, Proc. Natl. Acad. Sci. USA 87:1874-1878 [1990], hereinafter Guatelli).

Applicants note that the amendments made herein are intended to further their business interests and the prosecution of the present application in a manner consistent with the Patent Business Goals (P.B.G.)[1] while preserving the right to prosecute the original, or similar, claims in the future. None of the claim cancellations or additions made herein are intended to narrow the scope of the claims within the meaning of *Festo*[2] or related cases. None of the claim cancellations or addition made herein add new matter. Entry of the new claims and remarks is respectfully requested.

## I. Claims 90-106 are Definite

The Examiner has rejected Claims 90-106 as allegedly being indefinite "for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office action, pg 2). Each of the Examiner's rejections is addressed in order below.

### A. Claims 90, 99, and 101 are Definite

The Examiner states: "the phrase "target nucleic acid comprising first and second non-contiguous single-stranded regions separated by an intervening region comprising a double stranded region" is confusing. It is unclear whether the double stranded region of the intervening region is double stranded due to binding of the region to a complementary strand of nucleic acid such as a primer or due to the formation of secondary structure such as a hairpin structure." (Office Action, pg. 2). Applicants respectfully disagree and assert that the claims, as written, are clear. In particular, the Applicants point the Examiner to the definition of "target nucleic acid" provided in the specification (pg. 68, lines 21-25), which clearly states that the nucleic acid target may comprise single or double stranded DNA or RNA. Applicants respectfully submit that the means of obtaining the double stranded region is not relevant to an understanding of the method as written. Indeed, the nature of the double stranded region is not relevant to the subsequent

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1 65 Fed. Reg. 54603 (September 8, 2000).

2 *Festo Corp. v. Shokestu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558 (Fed. Cir. 2000) (en banc), *cert. granted.*

method steps. As such, the Applicants respectfully request that the rejection be withdrawn.

**B. Claims 90, 99, 101, 104, and 105 are Definite**

The Examiner has rejected Claims 90, 99, 101, 104, and 105 as allegedly being indefinite in the recitation of the phrase "capable of." Specifically, the Examiner argues that ""Capable of" is not an active method step, and may be interpreted to recite either a property of the oligonucleotides or a potential method of using the oligonucleotides." (Office action, pg. 3). Applicants must respectfully disagree. The phrase "capable of" appears in part (a) of Claims 90, 99, 101, 104, and 105 in the description of the oligonucleotide compositions provided in the method. The limitations recited after the phrase (*i.e.*, that the recited oligonucleotides are capable of binding to a portion of the target nucleic acid) describe characteristics of the compositions. As the phrase is not recited in a method step, it is unreasonable for the Examiner to assert that the phrase can be construed as a method of using the oligonucleotides.

Functional limitations are often used in claim construction in association with an element, ingredient, or step of a process to define a particular capability or purpose that is served by the recited element, ingredient, or step (*See*, MPEP 2173.05(g)). There is nothing inherently wrong with defining some part of an invention in functional terms (*See*, MPEP 2173.05(g)). For example, it was held that the limitation used to define a radical on a chemical compound as "incapable of forming a dye with said oxidizing developing agent," although functional, was perfectly acceptable because it set definite boundaries on the patent protection sought. *In re Barr*, 444 F.2d 588, 170 USPQ 33 (CCPA 1971). Likewise, the phrase "capable of binding" in the presently claimed invention sets definite boundaries. One skilled in the art recognizes that an oligonucleotide described as capable of binding a target nucleic acid will have certain features that define the oligonucleotide composition with respect to the target nucleic.

In order to further clarify the claimed subject matter and to further Applicants' business interests and the prosecution of the present application, yet without acquiescing to the Examiner's arguments, Applicants have amended Claim 90 recite the step of "mixing said target nucleic acid, said bridging oligonucleotide, said second oligonucleotide, and said cleavage means under conditions such that **a cleavage structure is formed from said target nucleic acid, said**

**bridging oligonucleotide, and said second oligonucleotide, and wherein** either said second oligonucleotide or said bridging oligonucleotide is cleaved" (emphasis added).[3]

"Cleavage structure" is defined in the Specification at page 71 lines 3-10 (*i.e.*, a structure with at least one region of duplex). As amended, Claim 90 recites that binding occurs. Independent Claim 99, as written, specifies that the bridging oligonucleotide hybridizes to the target to form an oligonucleotide/target complex. Independent claim 101 (and dependent claims 104 and 105) have been amended to specify that that the bridging oligonucleotide hybridizes to the target nucleic acid. For the above reasons, Applicants respectfully request that this rejection be withdrawn.

**C. Claim 90 is Definite**

The Examiner states "it is not readily apparent from the claim how the combination of the nucleic acid target, oligonucleotide probes, and cleavage agent result in the cleavage of the bridging oligonucleotide or the second oligonucleotide." (Office Action, pg. 3). Applicants respectfully disagree and submit that the claim, as written, is definite. Nonetheless, as described above, the claim has been amended to require that a cleavage structure is formed from said target nucleic acid, said bridging oligonucleotide, and said second oligonucleotide. As such, the claim specifically states how the combination of the nucleic acid target, oligonucleotide probes, and cleavage agent result in the cleavage of the bridging oligonucleotide or the second oligonucleotide. Thus, the rejection is moot and should be withdrawn.

**D. Claim 93 is Definite**

The Examiner states "the term "altered" is unclear because the nature and magnitude of the alteration made to the polymerase are not specified, nor is clear how the alterations relate to the method of claim 90." (Office Action, pg. 3). Applicants respectfully disagree. Nonetheless, in order to further clarify the claimed subject matter and to further Applicants' business interests and the prosecution of the present application, yet without acquiescing to the Examiner's

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[3] Applicants reserve the right to prosecute the original or similar claims in the future.

arguments, and preserving the right to prosecute the original (or similar) claims in the future, Applicants have amended Claim 93 recite "modified" rather than altered. The term "modified" is clearly defined in the specification (pg. 65, lines 18-27) as "a gene or gene product with displays modifications in sequence and or functional properties (i.e., altered characteristics) when compared to the wild type gene or gene product." As such, applicants respectfully submit that Claim 93 is definite and request that the rejection be withdrawn.

**E. Claims 93 and 121 are Definite**

The Examiner state "the phrase "derived from" is unclear because it is not defined in the specification." Applicants respectfully disagree and submit that the claim is clear as written. Nonetheless, in order to further clarify the claimed subject matter and to further Applicants' business interests and the prosecution of the present application, yet without acquiescing to the Examiner's arguments, and preserving the right to prosecute the original (or similar) claims in the future, the Applicants have amended claims 93 and 121 to remove the phrase "derived from." As such, the rejection is moot.

**F. Claims 95-97 are Definite**

The Examiner states "the term "define a region of overlap" lacks antecedent basis in Claim 90. Claim 90 does not describe the nature of the interactions among the target nucleic acid and the oligonucleotides." (Office Action, pg. 3). Applicants respectfully disagree and submit that the term does not lack antecedent basis. The specification describes overlap between two hybridizing oligonucleotides (pg. 96, line 14-24). In addition, Claim 90, as amended, specifies that the oligonucleotides anneal to form a cleavage structure. As such, Applicants respectfully request that the rejection be withdrawn.

**G. Claim 101 is Definite**

The Examiner states "The phrase "conditions such that said bridging oligonucleotide is modified to produce a modified oligonucleotide" lacks antecedent basis." Office Action, pg. 4. The Applicants respectfully disagree and submit that the claim, as written, has proper antecedent

basis. Nonetheless, in order to further clarify the claimed subject matter and to further Applicants' business interests and the prosecution of the present application, yet without acquiescing to the Examiner's arguments, and preserving the right to prosecute the original (or similar) claims in the future, Applicants have amended Claim 101 to state that the bridging oligonucleotide is modified by the reactant. As such, the rejection should be withdrawn.

**H. Claims 101 and 103 are Definite**

The Examiner states "it is not clear from the Claims how the bridging oligonucleotide is to be modified by a ligase. The structure of the complex formed by a target nucleic acid and a bridging oligonucleotide is not adequately defined, nor is it clear to what polynucleotide the bridging oligonucleotide will be ligated." Office action, pg. 4. The Applicants respectfully disagree. Claim 101, as presently written, defines the structure of the complex formed the target nucleic acid and the bridging oligonucleotide. In addition, the Applicants submit that the Examiner's argument that "nor is it clear to what polynucleotide the bridging oligonucleotide will be ligated" is not supportable. The claims do not require that the bridging oligonucleotide be ligated to a particular polynucleotide. It is thus improper for the Examiner to read this limitation into the claim and reject the claim based on such a limitation. Furthermore, the definitiveness of claim language must be analyzed in light of the specification, the prior art, and the knowledge of one skilled in the art (M.P.E.P. 2173.02). The use of ligation as a method of detecting structures formed by bridging oligonucleotides is described in the specification (pg. 97, lines 23-29). As such, the Applicants respectfully submit that Claim 101 and 103 are definite and request that the rejection be withdrawn.

**II. Claims 109 and 110 are Definite**

The Examiner states "The relevance of the 3' terminal nucleotide not complementary to the target nucleic acid is unclear." (Office Action, pg. 4). Applicants respectfully disagree and submit that the claims, as written, are clear. Claim 107, which claims 109 and 110 are dependent on, clearly describes the second oligonucleotide as "comprising a 3' portion and a 5' portion, wherein said 5' portion is completely complementary to..." The claim requires that the 5' portion

of the second oligonucleotide be completely complementary to the target sequence. The complementarity of the 3' region of the second oligonucleotide is further distinguished in depended claims 109 and 110 as comprising a 3' terminal nucleotide not complementary to said target nucleic acid (Claim 109) or consisting of a single nucleotide not complementary to the target nucleic acid. The Applicants respectfully submit that the Examiner is improperly applying a rejection under 35 U.S.C. 112, second paragraph, which states that "The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." M.P.E.P 2171. There is no requirement that the function of every claim element be explicitly spelled out in the claim. Furthermore, as described above, the definitiveness of claim language must be analyzed in light of the specification, the prior art, and the knowledge of one skilled in the art (M.P.E.P. 2173.02). The specification of the present invention clearly defines cleavage structures and the roles of first and second oligonucleotides in cleavage reactions (*See e.g.*, Specification, pgs. 95-97). As such, the Applicants respectfully submit that Claims 109 and 110 are definite and respectfully request that the rejection be withdrawn.

## III. Claims 111, 113, and 114 are Definite

The Examiner has rejected Claims 111, 113, and 114 under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states "Claim 107 does not recite the presence of a label necessary for the detection methods of claims 111, 113, or 114." (Office Action, pg. 5). Applicants respectfully disagree. Nonetheless, in order to further clarify the claimed subject matter and to further Applicants' business interests and the prosecution of the present application, yet without acquiescing to the Examiner's arguments, and preserving the right to prosecute the original (or similar) claims in the future, Applicants have amended Claims 111, 113, and 114 to include the element of a label. As such, Applicants respectfully request that the rejection be withdrawn.

## IV. Claim 123 is Definite

The Examiner has rejected Claim 123 under U.S.C. 112, second paragraph as allegedly being indefinite "for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Office Action, pg. 5. Each of the Examiner's rejections is addressed in order below. The Examiner states "The claim does not adequately describe the nature of the interaction between the two single stranded nucleic acid, the interactions among the non-target cleavage product and the two single stranded nucleic acid, or the structure of the complex formed by these nucleic acid fragments." Office Action, pg. 5. The Applicants respectfully disagree and submit that the claim adequately describes the nature of these interactions and the resulting structure. The Applicants remind the Examiner that the definiteness of the claims must not be examined in a vacuum, but must be analyzed in light of the specification (as well as the prior art and the opinion of one skilled in the art) (MPEP 2173.02). The Applicants direct the Examiner to the Specification, pg. 97, line 23 to pg. 98, line 4, where the use of protein binding to detect cleavage products is described. The Applicants respectfully submit that the claim is definite and request that the rejection be withdrawn.

The Examiner next states "the term "exposing" is not an active method step." (Office Action, pg. 5). Applicants respectfully disagree. Nonetheless, in order to further clarify the claimed subject matter and to further Applicants' business interests and the prosecution of the present application, yet without acquiescing to the Examiner's arguments, and preserving the right to prosecute the original (or similar) claims in the future, Applicants have amended Claim 123 to state "contacting" rather than exposing. As such, Applicants respectfully request that the rejection be withdrawn.

The Examiner further states "The nature of the binding of the protein to the oligonucleotide complex is not adequately described. It is unclear to which portion of the complex the protein binds, and whether this portion is single or double stranded." (Office Action, pg. 5). The Applicants respectfully disagree. Nonetheless, in order to further clarify the claimed subject matter and to further Applicants' business interests and the prosecution of the present application, yet without acquiescing to the Examiner's arguments, and preserving the right to prosecute the original (or similar) claims in the future, Applicants have amended Claim

123 to state that the cleavage product and the composition comprising a single-stranded portion of a protein binding region to form a double stranded protein binding region, and that the protein binds to the double stranded protein binding region.

The Examiner additionally states "The protein of step (a) (iii) lacks antecedent basis in step (a) (ii) because it is not specifically recited as the DNA binding protein that binds to the protein binding region of step (a) (ii)." Office Action, pg. 5. Applicants respectfully disagree and submit that Claim 123, as amended, clearly states the protein and the protein binding region to which it binds.

The Examiner further states "Step (b) lacks antecedent basis because it is not clearly recited how the hybridization of step (b) results in "detecting the cleavage of said cleavage structure" as recited in the preamble." Office Action, pg. 6. Applicants respectfully disagree and submit that Claim 123, as amended, clearly states how the hybridization of the cleavage product and the composition comprising a single-stranded portion of a protein binding region result in the detection of the cleavage product via binding of the protein. Applicants respectfully submit that Claim 123 is definite and request that the rejection be withdrawn.

## V. Claim 124 is Definite

The Examiner has rejected Claim 124 under U.S.C. 112, second paragraph as allegedly being indefinite "for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Office Action, pg. 6. The Examiner states "The phrase "nucleic acid producing protein" is unclear." (Office Action, pg. 6). The Applicants respectfully disagree. Nonetheless, in order to further clarify the claimed subject matter and to further Applicants' business interests and the prosecution of the present application, yet without acquiescing to the Examiner's arguments, and preserving the right to prosecute the original (or similar) claims in the future, Applicants have amended Claim 124 as suggested by the Examiner to recite "polymerase" rather than "nucleic acid producing protein." As such, Applicants respectfully request that the rejection be withdrawn.

## VI. Claim 127 is Definite

The Examiner has rejected Claim 127 under U.S.C. 112, second paragraph as allegedly being indefinite "for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Office Action, pg. 6. In particular, the Examiner states "the term "exposing" is not an active method step...." Office action, pg. 6. Applicants respectfully disagree. Nonetheless, in order to further clarify the claimed subject matter and to further Applicants' business interests and the prosecution of the present application, yet without acquiescing to the Examiner's arguments, and preserving the right to prosecute the original (or similar) claims in the future, Applicants have amended Claim 127 to recite "contacting" rather than exposing.

The Examiner further states "step (d) lacks antecedent basis because it is not clearly recited how the hybridization of step (d) results in "detecting the cleavage of said cleavage structure" as recited in the preamble." Applicants respectfully disagree and submit that the claim clearly describes the formation of a complex involving a cleavage product (step b) and the detection of this complex (and consequently the presence of the cleavage product) via the production of RNA transcripts (steps c and d). As such, the Applicants respectfully request that the rejection be withdrawn.

## VII. Claim 136 is Definite

The Examiner has rejected Claim 136 under U.S.C. 112, second paragraph as allegedly lacking antecedent basis. Office Action, pg. 6. In particular, the Examiner states that there is insufficient antecedent basis for the limitation "providing a third oligonucleotide complementary to a third portion of said target nucleic acid...wherein said third oligonucleotide is mixed with said reaction mixture in step b). Applicants respectfully disagree. Nonetheless, in order to further clarify the claimed subject matter and to further Applicants' business interests and the prosecution of the present application, yet without acquiescing to the Examiner's arguments, and preserving the right to prosecute the original (or similar) claims in the future, Applicants have amended Claim 136 to specify that the third oligonucleotide anneals to the third portion of the target nucleic acid. As such, the rejection should be withdrawn.

## VIII. Claims 107-136 are Non-Obvious

The Examiner has rejected Claims 107-136 under 35 U.S.C. 103(a) as allegedly being unpatentable over the '427 patent in view of the '503 patent, in further view of the '352 patent, in further view of Cole et al. in further view of Guatelli. Applicants must respectfully disagree and submit, in all cases, that the combination of references relied on by the Examiner fails to provide a *prima facie* showing of obviousness as required under § 2143 of the Manual of Patent Examining Procedure (MPEP). There are three criteria that must be met to provide *prima facie* obviousness. The first requirement is that there must be a suggestion or motivation in the references or the knowledge generally available to combine or modify the reference teachings. The second requirement is that the prior art must teach or suggest all the claim limitations. The third requirement is that should the proposed combination of references be carried out, that there is a reasonable expectation of success in carrying out the combination. Failure to establish any one of the three requirements precludes a finding of a *prima facie* case of obviousness, and, without more, entitles the Applicants to allowance of the claims at issue.[4] Applicants submit that the Examiner has failed to set forth a *prima facie* case of obviousness because these requirements have not been met.

In addressing this rejection, Applicants focus on independent claim 107 since the non-obviousness of independent claims necessarily leads to the non-obviousness of the claims dependent thereon (Claims 108-136).[5] The Examiner rejects independent Claim 107 as being obvious in light of the '427 and the '503 patents (Office Action, pg. 9). The Applicants respectfully disagree and submit that Claim 107 is not obvious because the '427 and '503 patents do not teach all of the element of Claim 107 and the '427 and '503 patents provide no motivation within the patents to combine their teaching to yield the method of Claim 107. In particular, neither the '427 nor the '503 patents teach the claim element of Hepatitis C virus target nucleic acid. In fact, the Examiner admits, in reference to the '427 and '503 patents, that "[t]hey do not specifically teach the use of the method to detect hepatitis virus (HCV). (Office Action, pg. 9).

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4 *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990).

5 §MPEP 2143.03.

The Examiner attempts to remedy this lack of teaching by stating

> "However, it would have been obvious to one of ordinary skill in the art at the time the application was filed to adapt the method for the detection of HCV nucleic acid based on the known ability of the method to detect a broad range of RNA and DNA viruses (USPN '427 Column 2, lines 15-17) and the known importance of HCV as a major human pathogen in order to derive a rapid and sensitive assay for the detection of HCV infection" (Office Action, pg. 9).

Applicants submit that the case law is clear that any teaching or suggestion to combine or modify references must be found in the reference(s) themselves or in the knowledge available to one of ordinary skill in the art. They may not, as the Examiner has attempted to do, be derived from the applicant's disclosure (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The Examiner is reminded, that under the law, an Examiner is not one skilled in the art and that consequently, the Examiner's opinion as to what one skilled in the art might believe is not sufficient support for a motivation to modify the teachings of the cited references (See, *In re Rijckaert,* 9 F.3d 1531, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993)). When a rejection is based on facts within the personal knowledge of the examiner, the facts must be supported by an affidavit from the examiner (M.P.E.P. 2144.03). The Applicants submit that the Examiner has failed to point to a teaching in the references cited to modify the teachings of the cited reference to provide a method comprising a Hepatitis C target nucleic acid. As such, the Applicants request that the rejection be withdrawn.

In addition, the Applicants submit that the Examiner has provided no teaching or suggestion for combining the cited references to yield the method of Claim 107. The Examiner states "It would have been obvious to one of ordinary skill in the art at the time the application was filed to combine the structure-based virus detection assay of USPN '427 with the formation of binding site for a cleavage agent as taught in USPN '503 to allow a simple means for the detection of the oligonucleotide/target nucleic acid structure." (Office Action, pg. 9). The Applicants respectfully disagree and submit that the Examiner has failed to provide a motivation to combine the '427 and '503 patents. Applicants submit that the Examiner has not provided sufficient evidence of a suggestion or motivation for making the cited combination. When applying 35 U.S.C. § 103, the cited references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination. See *In re Fine*, 837 F.2d

1071, 1074. Further, references cannot be considered collectively until the Examiner points to some motivation to combine the cited references.[6] The purpose of this threshold requirement is to prevent the Examiner from using the invention itself and hindsight reconstruction to defeat the patentability of the invention (*In re Rouffet et al.*, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). The Examiner has failed to show reasons why a skilled artisan confronted with the same problems would make the combination cited by the Examiner. Indeed, the two references do not contain any motivation or suggestion to combine the teachings. The '427 patent does not provide any teaching or suggestion for how one would adapt the disclosed cooperative oligonucleotide to form a cleavage structure. Likewise, the '503 patent provides no teaching or suggestion for using the disclosed probes for the detection of HCV target nucleic acid.

In conclusion, the Applicants submit that the Examiner has failed to provide a prima facie case of obviousness because 1) the Examiner has pointed to no suggestion or motivation within the references to combine the references; and 2) even if the references are improperly combined, they do not teach all of the elements of Claim 107.

**CONCLUSION**

All grounds of rejection and objection of the Office Action of July 18, 2002 having been addressed, reconsideration of the application is respectfully requested. It is respectfully submitted that the claims should be allowed. Should the Examiner have any questions, or if a telephone conference would aid in the prosecution of the present application, Applicant encourages the Examiner to call the undersigned collect at 608-218-6900.

Dated: November 27, 2002

David A. Casimir
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6 *Hodash v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143, n. 5, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986).

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**Appendix 1**

**Version With Markings To Show Changes Made**

**In The Claims:**

Please amend the following claims as follows:

90. A method, comprising:

a) providing:

i) target nucleic acid comprising first and second non-contiguous single-stranded regions separated by an intervening region comprising a double-stranded region, wherein said target nucleic comprises at least a portion of Hepatitis C virus nucleic acid;

ii) a bridging oligonucleotide capable of binding to said first and second non-contiguous single-stranded regions;

iii) a second oligonucleotide capable of binding to a portion of said first non-contiguous single-stranded region; and

iii) a cleavage agent;

b) mixing said target nucleic acid, said bridging oligonucleotide, said second oligonucleotide, and said cleavage agent under conditions such that a cleavage structure is formed from said target nucleic acid, said bridging oligonucleotide, and said second oligonucleotide, and wherein either said second oligonucleotide or said bridging oligonucleotide is cleaved by said cleavage agent.

93. The method of Claim 92, wherein said thermostable 5' nuclease comprises a[n] [altered] modified polymerase; wherein said modified polymerase is a modified [derived from a] native polymerase[s] of *Thermus* species.

101. A method, comprising:

a) providing:

i) target nucleic acid comprising first and second non-contiguous single-stranded regions separated by an intervening region comprising a double-stranded portion, wherein said target nucleic acid comprises at least a portion of Hepatitis C virus nucleic acid;

ii) a bridging oligonucleotide capable of binding to said first and second non-contiguous single-stranded regions; and

iii) a reactant selected from the group consisting of polymerases and ligases; and

b) mixing said target nucleic acid, said bridging oligonucleotide and said reactant under conditions such that said bridging oligonucleotide hybridizes to said target nucleic acid, and wherein said bridging oligonucleotide is modified by said reactant to produce a modified oligonucleotide.

111. The method of Claim 107, wherein either said first oligonucleotide or said second oligonucleotide comprises a fluorescent label and said detecting the cleavage of said cleavage structure comprises detection of fluorescence from said fluorescent label.

113. The method of Claim 107, wherein said first and second oligonucleotides collectively comprise a fluorescence energy donor and a fluorescence energy acceptor and wherein said detecting the cleavage of said cleavage structure comprises detection of fluorescence energy transfer between said fluorescence energy donor and said fluorescence energy acceptor.

114. The method of Claim 107, wherein said either said first oligonucleotide or said second oligonucleotide comprises a label selected from the group consisting of a radioactive label, a luminescent label, a phosphorescent label, a fluorescence polarization label, and charge

label, and detecting the cleavage of said cleavage structure comprises detection selected from the group consisting of detection of radioactivity, luminescence, phosphorescence, fluorescence polarization, and charge from said label.

121. The method of Claim 120, wherein a portion of the amino acid sequence of said nuclease is homologous to a portion of the amino acid sequence of a thermostable DNA polymerase [derived] from a thermophilic organism.

123. The method of Claim 107, wherein said detecting the cleavage of said cleavage structure comprises:

a) providing:

i) said non-target cleavage product;

ii) a composition comprising two single-stranded nucleic acids annealed so as to define a single-stranded portion of a protein binding region; and

iii) a protein; and

b) [exposing] contacting said non-target cleavage product [to] and said single-stranded portion of said protein binding region under conditions such that said non-target cleavage product and said single-stranded portion of a protein binding region hybridize to form a double stranded protein binding region, and wherein said protein binds to said double stranded protein binding region.

124. The method of Claim 123, wherein said protein comprises a nucleic acid [producing protein] polymerase and wherein said nucleic acid [producing protein] polymerase binds to said protein binding region and produces nucleic acid.

127. The method of Claim 107, wherein said detecting the cleavage of said cleavage structure comprises:

a) providing:

i) said non-target cleavage product;

ii) a single continuous strand of nucleic acid comprising a sequence defining a single strand of an RNA polymerase binding region;

iii) a template-dependent DNA polymerase; and

iv) a template-dependent RNA polymerase;

b) [exposing] contacting said non-target cleavage product [to] and said RNA polymerase binding region under conditions such that said non-target cleavage product binds to a portion of said single strand of said RNA polymerase binding region to produce a bound non-target cleavage product;

c) [exposing] contacting said bound non-target cleavage product [to] and said template-dependent DNA polymerase under conditions such that a double-stranded RNA polymerase binding region is produced; and

d) [exposing] contacting said double-stranded RNA polymerase binding region [to] and said template-dependent RNA polymerase under conditions such that RNA transcripts are produced.

136. The method of Claim 107, further comprising providing a third oligonucleotide complementary to a third portion of said target nucleic acid upstream of said first portion of said first target nucleic acid, wherein said third oligonucleotide is mixed with said reaction mixture in step b); and wherein said third oligonucleotide is annealed to said third portion of said target nucleic acid.

**Appendix 2**

**Pending Claims**

90. A method, comprising:

a) providing:

i) target nucleic acid comprising first and second non-contiguous single-stranded regions separated by an intervening region comprising a double-stranded region, wherein said target nucleic comprises at least a portion of Hepatitis C virus nucleic acid;

ii) a bridging oligonucleotide capable of binding to said first and second non-contiguous single-stranded regions;

iii) a second oligonucleotide capable of binding to a portion of said first non-contiguous single-stranded region; and

iii) a cleavage agent;

b) mixing said target nucleic acid, said bridging oligonucleotide, said second oligonucleotide, and said cleavage agent under conditions such that a cleavage structure is formed from said target nucleic acid, said bridging oligonucleotide, and said second oligonucleotide, and wherein either said second oligonucleotide or said bridging oligonucleotide is cleaved by said cleavage agent.

91. The method of Claim 90, wherein said cleavage agent comprises a nuclease.

92. The method of Claim 91, wherein said cleavage agent comprises a thermostable 5' nuclease.

93. The method of Claim 92, wherein said thermostable 5' nuclease comprises a modified polymerase; wherein said modified polymerase is a modified native polymerase of *Thermus* species.

94. The method of Claim 91, wherein said nuclease is selected from the group consisting of *Pyrococcus woesii* FEN-1 endonuclease, *Methanococcus jannaschii* FEN-1 endonuclease, *Pyrococcus furiosus* FEN-1 endonuclease, and *Archaeoglobus fulgidus* FEN-1 endonuclease.

95. The method of Claim 90, wherein said conditions of said mixing allow for hybridization of said bridging oligonucleotide and said second oligonucleotide to said target nucleic acid so as to define a region of overlap of said oligonucleotides.

96. The method of Claim 95, wherein said region of overlap comprises one base.

97. The method of Claim 95, wherein said region of overlap comprises more than one base.

98. The method of Claim 90, wherein said Hepatitis C virus is selected from the group consisting of Hepatitis C virus variants 1a, 1b, 2a/c, and 3a.

99. A method, comprising:

a) providing:

i) target nucleic acid comprising first and second non-contiguous single-stranded regions separated by an intervening region, said intervening region comprising a first double-stranded portion and a second double-stranded portion separated by a connecting single-stranded portion, wherein said target nucleic acid comprises at least a portion of Hepatitis C virus nucleic acid; and

ii) a bridging oligonucleotide capable of binding to said first and second non-contiguous single-stranded regions; and

b) mixing said target nucleic acid and said bridging oligonucleotide under conditions such that said bridging oligonucleotide hybridizes to said target to form an oligonucleotide/target complex.

100. The method of Claim 99, wherein said Hepatitis C virus is selected from the group consisting of Hepatitis C virus variants 1a, 1b, 2a/c, and 3a.

101. A method, comprising:

a) providing:

i) target nucleic acid comprising first and second non-contiguous single-stranded regions separated by an intervening region comprising a double-stranded portion, wherein said target nucleic acid comprises at least a portion of Hepatitis C virus nucleic acid;

ii) a bridging oligonucleotide capable of binding to said first and second non-contiguous single-stranded regions; and

iii) a reactant selected from the group consisting of polymerases and ligases; and

b) mixing said target nucleic acid, said bridging oligonucleotide and said reactant under conditions such that said bridging oligonucleotide hybridizes to said target nucleic acid, and wherein said bridging oligonucleotide is modified by said reactant to produce a

modified oligonucleotide.

102. The method of Claim 101, wherein said reactant is a polymerase, and said modified oligonucleotide comprises an extended oligonucleotide.

103. The method of Claim 101, wherein said reactant is a ligase, and said modified oligonucleotide comprises a ligated oligonucleotide.

104. The method of Claim 101, wherein said bridging oligonucleotide is capable of binding to fewer than ten nucleotides of each of said first and second non-contiguous single-stranded regions.

105. The method of Claim 104, wherein said bridging oligonucleotide is capable of binding to seven or fewer nucleotides of each of said first and second non-contiguous single-stranded regions.

106. The method of Claim 101, wherein said Hepatitis C virus is selected from the group consisting of Hepatitis C virus variants 1a, 1b, 2a/c, and 3a.

107. A method for detecting the presence of a target nucleic acid molecule by detecting non-target cleavage products comprising:

a) providing:

i) a cleavage agent;

ii) Hepatitis C virus target nucleic acid, said target nucleic acid comprising a first region and a second region, said second region downstream of and contiguous to said first region;

iii) a first oligonucleotide, wherein at least a portion of said first oligonucleotide is completely complementary to said first portion of said first target nucleic acid;

iv) a second oligonucleotide comprising a 3' portion and a 5' portion,

wherein said 5' portion is completely complementary to said second portion of said target nucleic acid;

b) mixing said cleavage agent, said target nucleic acid, said first oligonucleotide and said second oligonucleotide to create a reaction mixture under reaction conditions such that at least said portion of said first oligonucleotide is annealed to said first region of said target nucleic acid and wherein at least said 5' portion of said second oligonucleotide is annealed to said second region of said target nucleic acid so as to create a cleavage structure, and wherein cleavage of said cleavage structure occurs to generate non-target cleavage product; and

c) detecting the cleavage of said cleavage structure.

108. The method of Claim 107, wherein said detecting the cleavage of said cleavage structure comprises detecting said non-target cleavage product.

109. The method of Claim 107, wherein said 3' portion of said second oligonucleotide comprises a 3' terminal nucleotide not complementary to said target nucleic acid.

110. The method of Claim 107, wherein said 3' portion of said second oligonucleotide consists of a single nucleotide not complementary to said target nucleic acid.

111. The method of Claim 107, wherein either said first oligonucleotide or said second oligonucleotide comprises a fluorescent label and said detecting the cleavage of said cleavage structure comprises detection of fluorescence from said fluorescent label.

112. The method of Claim 107, wherein said detecting the cleavage of said cleavage structure comprises detection of mass.

113. The method of Claim 107, wherein said first and second oligonucleotides collectively comprise a fluorescence energy donor and a fluorescence energy acceptor and

wherein said detecting the cleavage of said cleavage structure comprises detection of fluorescence energy transfer between said fluorescence energy donor and said fluorescence energy acceptor.

114. The method of Claim 107, wherein said either said first oligonucleotide or said second oligonucleotide comprises a label selected from the group consisting of a radioactive label, a luminescent label, a phosphorescent label, a fluorescence polarization label, and charge label, and detecting the cleavage of said cleavage structure comprises detection selected from the group consisting of detection of radioactivity, luminescence, phosphorescence, fluorescence polarization, and charge from said label.

115. The method of Claim 107, wherein said first oligonucleotide is attached to a solid support.

116. The method of Claim 107, wherein said second oligonucleotide is attached to a solid support.

117. The method of Claim 107, wherein said cleavage agent comprises a structure-specific nuclease.

118. The method of Claim 117, wherein said structure-specific nuclease comprises a thermostable structure-specific nuclease.

119. The method of Claim 118, wherein said cleavage agent comprises a 5' nuclease.

120. The method of Claim 119, wherein said 5'-nuclease comprises a thermostable 5'-nuclease.

121. The method of Claim 120, wherein a portion of the amino acid sequence of said

nuclease is homologous to a portion of the amino acid sequence of a thermostable DNA polymerase from a thermophilic organism.

122. The method of Claim 121, wherein said thermophilic organism is selected from the group consisting of *Thermus aquaticus*, *Thermus flavus*, and *Thermus thermophilus*.

123. The method of Claim 107, wherein said detecting the cleavage of said cleavage structure comprises:

a) providing:

i) said non-target cleavage product;

ii) a composition comprising two single-stranded nucleic acids annealed so as to define a single-stranded portion of a protein binding region; and

iii) a protein; and

b) contacting said non-target cleavage product and said single-stranded portion of said protein binding region under conditions such that said non-target cleavage product and said single-stranded portion of a protein binding region hybridize to form a double stranded protein binding region, and wherein said protein binds to said double stranded protein binding region.

124. The method of Claim 123, wherein said protein comprises a nucleic acid polymerase and wherein said nucleic acid polymerase binds to said protein binding region and produces nucleic acid.

125. The method of Claim 124, wherein said protein binding region is a template-dependent RNA polymerase binding region.

126. The method of Claim 125, wherein said template-dependent RNA polymerase binding region is a T7 RNA polymerase binding region.

127. The method of Claim 107, wherein said detecting the cleavage of said cleavage structure comprises:

a) providing:

i) said non-target cleavage product;

ii) a single continuous strand of nucleic acid comprising a sequence defining a single strand of an RNA polymerase binding region;

iii) a template-dependent DNA polymerase; and

iv) a template-dependent RNA polymerase;

b) contacting said non-target cleavage product and said RNA polymerase binding region under conditions such that said non-target cleavage product binds to a portion of said single strand of said RNA polymerase binding region to produce a bound non-target cleavage product;

c) contacting said bound non-target cleavage product and said template-dependent DNA polymerase under conditions such that a double-stranded RNA polymerase binding region is produced; and

d) contacting said double-stranded RNA polymerase binding region and said template-dependent RNA polymerase under conditions such that RNA transcripts are produced.

128. The method of Claim 127, further comprising the step of e) detecting said RNA transcripts.

129. The method of Claim 127, wherein said template-dependent RNA polymerase is T7 RNA polymerase.

130. The method of Claim 107, wherein said target nucleic acid comprises single-stranded DNA.

131. The method of Claim 107, wherein said target nucleic acid comprises double-stranded DNA and prior to step c), said reaction mixture is treated such that said

double-stranded DNA is rendered substantially single-stranded.

132. The method of Claim 131, wherein said double-stranded DNA is rendered substantially single-stranded by heat.

133. The method of Claim 107, wherein said reaction conditions comprise providing a source of divalent cations.

134. The method of Claim 133, wherein said divalent cation is selected from the group consisting of $Mn^{2+}$ and $Mg^{2+}$ ions.

135. The method of Claim 107, wherein said first and said second oligonucleotides are provided in concentration excess compared to said target nucleic acid.

136. The method of Claim 107, further comprising providing a third oligonucleotide complementary to a third portion of said target nucleic acid upstream of said first portion of said first target nucleic acid, wherein said third oligonucleotide is mixed with said reaction mixture in step b); and wherein said third oligonucleotide is annealed to said third portion of said target nucleic acid.